Case Report / *Olgu Sunumu*

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A case of Severe Low-dose Methotrexate-induced Toxicity

Düşük Doz ile Ortaya Çıkan Şiddetli Metotreksat Toksisitesi: Bir Olgu Sunumu

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Abstract

Methotrexate (MTX) is an antimetabolite which competitively inhibits dihydrofolic acid reductase; inhibits purine and thymidylic acid synthesis, which in turn interferes with DNA synthesis, repair, and cellular replication. MTX is a good treatment option for neoplastic, rheumatic and dermatological diseases. However, rarely, may cause side effects, such as agranulocytosis and bone marrow suppression, mucosal tissue inflammation and necrotic changes, liver cell necrosis and hepatic cirrhosis, pulmonary fibrosis, and severe renal dysfunction. Herein, we report a 67-year-old female patient with a history of psoriasis for 15 years and MTX 15 mg/sc/week use for 8 years who was admitted due to the complaints of pancytopenia, mucositis and ulcers on psoriatic plaques despite low-dose MTX use. We present this case to remind that MTX toxicity might occur with low-dose MTX usage and to draw attention to various factors that facilitate the low-dose MTX toxicity, such as age, renal insufficiency, low albumin levels, infections, proton pump inhibitors and non-steroidal anti-inflammatory drugs.

Keywords: Methotrexate toxicity, mucositis, ulcer

Öz

Metotreksat (MTK), dihidrofolat redüktaz enzimini kompetitif olarak inhibe ederek, pürin ve timidin sentezini bozan ve DNA sentezini inhibe eden antimetabolit bir ilaçtır. Onkolojik, romatolojik ve dermatolojik hastalıkların tedavisinde yaygın olarak kullanılan iyi bir tedavi ajanıdır. Fakat nadiren agranülositoz, kemik iliği süpresyonu, mukozal doku enflamasyonu ve nekrotik değişiklikler, karaciğer hücre nekrozu, siroz, pulmoner fibroz ve böbrek yetmezlik gibi ciddi yan etkilere neden olabilir. Bu olguda, 15 yıldır psoriasis tanısı olan, sekiz yıldır 15 mg/hafta subkutanöz yolla MTK kullanan, 67 yaşında bir kadın hasta, düşük doz MTK kullanmasına rağmen ortaya çıkan pansitopeni, mukozit ve psoriyatik plaklar üzerinde gelişen ülserler nedeniyle sunulmaktadır. Amacımız MTK toksisitesinin düşük doz kullanımı ile de ortaya çıkabileceğini hatırlatmak ve MTK toksisitesini kolaylaştıran; yaş, renal yetmezlik, düşük albümin düzeyi, enfeksiyonlar, proton pompa inhibitörü ve non-steroid anti-enflamatuvar ilaçlar gibi çeşitli faktörlere dikkat çekmektir.

Anahtar Sözcükler: Metotreksat toksisitesi, mukozit, ülser

Introduction

Methotrexate (MTX) is an effective but potentially toxic antimetabolite anticancer drug which has been in use since 1960s (1,2). Low-dose MTX therapy used in psoriasis rarely causes toxicity (3). A 67-year-old female patient, who had chronic plaque-type psoriasis for 15 years and has been used MTX 15 mg/sc/week for eight years, presented with ulcerations of psoriatic plaques on the chest and back, oral ulcers and pancytopenia. The diagnosis of low-dose MTX-induced toxicity was established.

Case

A 67-year-old female patient with a 15-year history of psoriasis was admitted to our hospital with a one week history of painful ulcers on psoriatic plaques and oral ulcers. It was learned from the patient's history that she had been using 15 mg MTX injection weekly for eight years without any side effects. She reported non-adherence to medication occasionally. She had been taking drugs for hypertension and diabetes for the past 25 years. Other home medications included a proton pump inhibitor

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(PPI) (lansoprazole) and non-steroidal anti-inflammatory drugs (NSAIDs). Physical examination revealed confluent, shallow ulcerations covered by yellow fibrin or brown slough along the intermamarial area and buttocks on the declining psoriatic plaques (Figure 1). During the oral examination, ulcers and erosions, some of them covered with white membrane, on the buccal mucosa and tongue were noted (Figure 2).

A skin biopsy revealed changes consistent with MTX toxicity, including diffuse epidermal necrosis, acanthotic and spongiotic epidermis with overlying parakeratosis and scattered dyskeratotic keratinocytes. A mild superficial and perivascular lymphocytic infiltrate with rare eosinophils was detected within the dermis, underlying the ulcer. Fibroblast proliferation extended all the way into the subcutaneous septae (Figure 3). No evidence of infectious process or vasculitis was seen. Periodic acid-schiff was negative for fungi.

Laboratory studies revealed pancytopenia with a white blood cell count of 2.31 K/µL, platelet count of 33 K/µL, hemoglobin of 9.5 g/dL, hematocrit value of 28.3%, and absolute neutrophil count of 1.6 K/µL. Her creatinine and liver enzymes slightly elevated while serum albumine was low. MTX blood level was 0.04 µmol/L. Urinary tract infection was detected. Laboratory testing results are shown in Table 1. The patient was started on intravenous fluids and daily oral folic acid, and MTX was held. Her renal function returned to baseline after receiving fluids and her skin began to re-epithelialize. Blood counts began to normalize on day 7. Treatment was supportive.

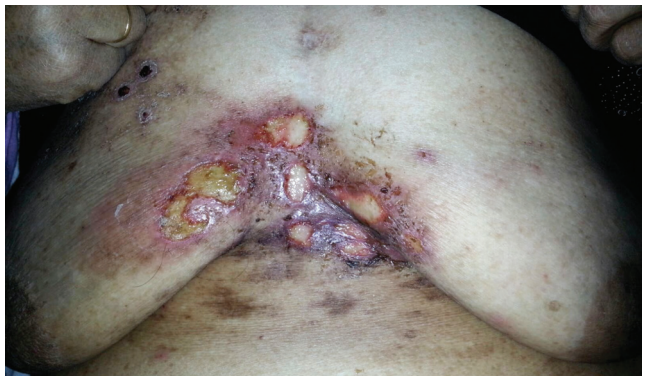

Figure 1. Shallow ulcers located on the psoriasis plaques over the intermammarial region

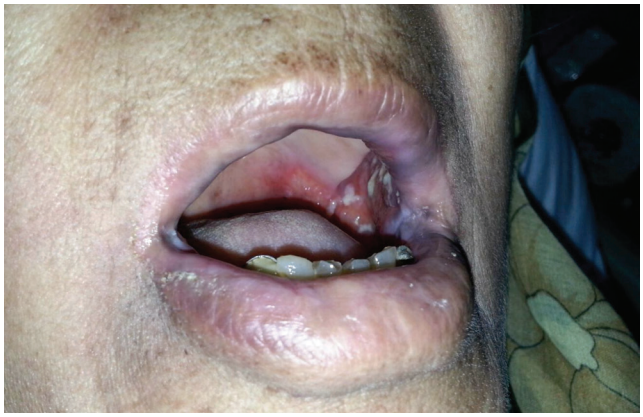

Figure 2. Ulcers and erosions, some with white membrane, on the buccal mucosa

Discussion

MTX is an antifolate agent used as a mainstay of treatment for psoriasis and rheumatoid arthritis because of its efficacy and long track record of safety (4). The most common minor adverse events associated with low-dose MTX use are stomatitis, headaches, nausea, fatigue, and anorexia (5,6). While hepatotoxicity has historically been the most feared side effect, pancytopenia is now emphasized as the most serious adverse event. It has been observed in approximately 1.5% of patients taking low-dose MTX (4,6,7). Psoriatic plaque erosion is a rare cutaneous manifestation of low-dose MTX toxicity with unknown prevalence and has been hypothesized that a painful erosion of psoriatic plaque is an early cutaneous sign of pancytopenia (8).

The most common risk factors for psoriatic plaque erosion are being the initiation or reinstatement of MTX after a drug hiatus, an increase in the MTX dose, renal impairment, and the use of NSAIDs or aspirin. Age >55, folate deficiency, low serum albumin level, and drug-drug interactions are also common risk factors (Table 2) (5,7,8).

Drug-drug interactions are key contributors to toxicity (Table 2). NSAIDs (drug retention), aspirin sulfonamides, penicillin, and colchicines (decreases MTX clearance), barbiturates, nitrofurantoin (impair folate absorption), trimethoprim-sulfamethoxazole, triamterene, pyrimethamine, ethanol (inhibit the enzyme dihydrofolate reductase) phenytoin, probenecid,

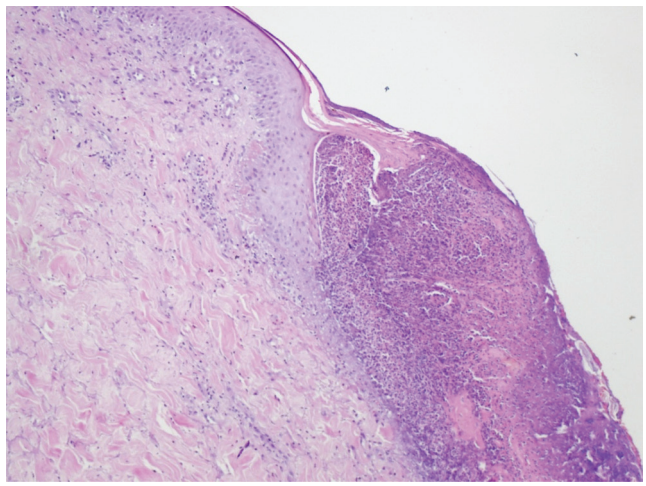

Figure 3. Histological changes consistent with methotrexate toxicity (Hematoxylin&eosin, x20)

salicylates, sulfonamides, tetracycline, chloramphenicol, sulfonylureas (displace MTX from albumin), PPIs (the renal excretion of MTX) are the main accused drugs (4,5,7,9).

Table 1. Laboratory testing results of the patient

WBC: 2.31 U/L	Glucose: 128 mg/dL
RBC: 3.38 U/L	Urea: 82.4 mg/dL
MCV: 83.8 FL	Creatine: 1.96 mg/dL
MCHC: 33.4 G/DL	Cholesterol: 147 mg/dL
HBG: 9.5 G/DL	Triglyceride: 122 mg/dL
HCT: 28.3%	AST: 93 U/L
RDW: 14.8%	ALT: 99 U/L
PLT: 33 10 E9/	GGT: 29.7 U/L
NEU: 1.68 10 E9/L	LDH: 213.7 U/L
LYM: 0.32 10 E9/L	Albumin: 3.1 g/dL
MON: 0.06 10 E9/L	Total protein: 7.2 g/dL
PDW: 16.4 GSD	Direct bilirubin: 0.4 mg/dL
	Total bilirubin: 1.3 mg/dL
	CRP: 202 mg/dL
	Ferritin: 744 mg/mL
	Sedimentation: 111 mm/hour
	Urine tests: (++++) leukocyte
	MTX doses on blood: 0.04 umol/L

WBC: White blood cells, RBC: Red blood cells, MCV: Mean corpuscular volüme, MCHC: Mean corpuscular hemoglobin concentration, HBG: Hemoglobin, HCT: Hematocrit, RDW: Red cell distribution width, PLT: Platelet, LYM: Lymphocyte, PDW: Platelet distrubition width, AST: Aspartate transaminase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, MTX: Methotrexate

Table 2. Risk factors for methotrexate toxicity

Age >55	Drug-drug Interactions
Alteration of methotrexate dose	Non-steroidal anti-inflammatory drugs
Renal Impairment	Salisylates (aspirin)
Low serum albumine	Sulfonamides
Infection	Phenytoin
Psoriatic flare	Probenecid
Folate deficiency	Tetracycline, Chloramphenicol
	Sulfonylureas
	Penicillin
	Colchicine
	Ciprofloxacin
	Barbirutares
	Nitrofurantoin
	Ethanol
	Diuretics
	Proton pump inhibitors

In conclusion, we describe a patient with a rare presentation of low-dose MTX toxicity. Our patient's risk factors for MTX toxicity were age, low serum albumine level, urinary tract infection, irregular use of MTX, renal impairment, and PPIs and NSAIDs usage. Particularly in elderly patients, risk factors for MTX intoxicity, especially drugs should be evaluated thoroughly. As it was in our case, PPIs and/or NSAIDs usage is a risk factor for MTX toxicity that we can easily overlook.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and Internally peer-reviewed.

Authorship Contributions

Concept: Filiz Topaloğlu Demir. Design: Filiz Topaloğlu Demir. Data Collection or Processing: Yavuz Tezcan, Şerife Başaran. Analysis or Interpretation: Filiz Topaloğlu Demir. Literature Search: Zafer Türkoğlu. Writing: Filiz Topaloğlu Demir.

Conflict of Interest: No conflict of interest was declared by the authors.

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